Blood Brain Barrier: The Role of Calcium Homeostasis

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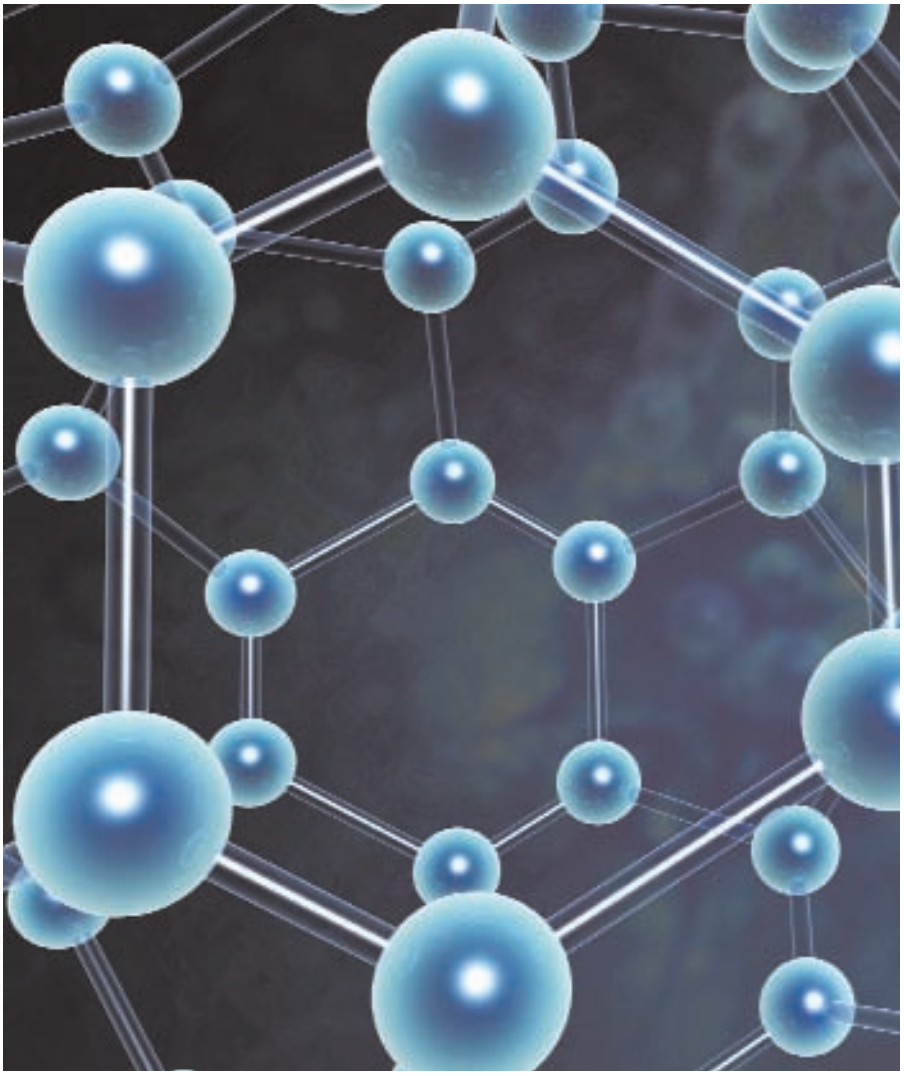
ABSTRACT

Calcium as a molecule plays a significant role in the body, especially in the central nervous system. In its free form, it has been classified as a cofactor, second messenger, and signaling molecule, and, when bound, forms a protein and coenzyme. This is secondary to the critical, and at times, very sensitive reactions associated with it. Calcium homeostasis, especially in the context of the central nervous system, may have crucial implications in many neuropsychiatric conditions. The hypothesis presented will explore the link between the blood-brain barrier (BBB) and calcium homeostasis (CH) as it is a complex, physiological process. Absence of organic deficits associated with conditions, such as pervasive developmental disorder (PDD), autism spectrum disorders (ASD), mental retardation (MR), and attention deficit hyperactivity disorder (ADHD), in addition to other chronic psychiatric disorders, builds a more compelling case to explore CH in context of the BBB.



CALCIUM HOMEOSTASIS (CH): WHAT IS IT?

Experimental evidence[1] points to age-related variations in the brains of rodents in response to artificially induced hypercalcemia. According

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to the study, levels of cerebrospinal fluid calcium in relationship to total brain calcium remains constant in adult rats despite experimentally induced hypercalcemia. However, that was not the case with neonatal and postnatal rodent brains, suggesting a role for developmentally altered CH. Calcium is tightly regulated within the extracellular and intracellular compartments of the central nervous system, involving processes that include transport mechanisms across the blood brain barrier (BBB) and cellular membranes, extensive binding by proteins and other macromolecules, and sequestration within a variety of intracellular organelles.[2] Estimates suggestive of steady-state whole brain calcium range between 3.5 and 5 micromoles/gm.[3–6] On the other hand, estimates of basal free cytoplasmic calcium concentration in neuronal cultures suggest levels as low as 0.1 micromoles/gm.[7,8] To further understand the physiology/kinetics of central nervous system calcium, one should consider the compartmental model of brain calcium.[9–11] Basically, according to the existing theories, there are a total of five compartments starting from outer free calcium in the extra cellular space or ECS (~10%), loosely associated extracellular plasma membrane calcium (~55%), the intracellular compartment with moderate avidity (~17%), a tightly bound, non-exchangeable intracellular compartment (~15%), and free cytoplasmic calcium (<0.01%).

BLOOD BRAIN BARRIER: WHAT IS IT?

There is abundant calcium in the brain, with tissue amounts ranging to approximately 250 percent of an equivalent volume of extracellular fluid. Despite the volumes, it is very tightly regulated within several compartments, which serve as "buffers" between the inner free cytoplasmic calcium and outer free extracellular space calcium. According to estimates, for every free atom of calcium in the cytoplasm, 1000 to 3500 atoms are either bound or sequestered.

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The BBB, however, plays an important role in regulating outer extracellular space calcium and is crucial in maintaining normal physiologic function by modulating rapid equilibrium with tissue calcium.[12] Therefore, the BBB and calcium regulation/homeostasis demand closer attention in neuropsychiatry than was previously thought.

The BBB is highly selective and controls the passage of substances in and out of the central nervous system. Essentially, the BBB comprises a confluent layer of microvascular endothelial cells lining the capillaries intertwined by astrocytic processes forming tight junctions in the brain. By some estimates, the human brain may have on the order of 100 million capillaries with a surface area of approximately 12 meters squared.[12,13] Nearly every neuron in the brain has its own capillary, with an average distance from capillary to neuron of 8 to 20 micromillimeters.[14] Thus, the BBB controls the delivery of many macromolecules, i.e., proteins, drugs, and other essential components to the brain.[15] While smaller molecules and lipid soluble proteins cross the BBB easily, larger ones need receptor-mediated transcytosis to enter the CNS. The calcium molecule is ubiquitous, in free, bound, and loosely or partially bound forms interchanging to maintain equilibrium/homeostasis in the normal human brain.

DISCUSSION

The link. Despite advances in psychopharmacology and enhanced diagnostic modalities, the multifactorial etiologies of various neuropsychiatric conditions continue to challenge the scientific community. The neurophysiology of calcium poses a significant challenge considering its complex/global role in neurometabolic and neurodegenerative conditions. Although large amounts of literature in the field have become available individually, we will explore the relevance of a compromised BBB and its pertinence to altered calcium homeostasis. Especially of note would be site-specific pathology (i.e., the dorsolateral prefrontal cortex [DLPFC] in schizophrenia [SCH] and bipolar disorder [BD], the frontostriatal system in Tourette's syndrome [TS], the lateral fusiform gyrus in autism spectrum disorders, the hypothalamus in neuroleptic malignant syndrome [NMS], the amygdala in adult autism, and more global spread in age-related neurodegenerative diseases, such as Alzheimer's dementia [AD]). At this time, we can only speculate about the link of site-specific

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compromise of the BBB and altered calcium homeostasis in the context of neuropsychiatric conditions.

Let's begin with four existing models, which include developmental, early childhood/adolescence, early adulthood, and aging and metabolic conditions.

Developmental. Maternal calcium levels are associated with fetal development and hypothetically may have irreversible impact on the growth of an individual.[16] Experimental studies report that functional systems of organisms develop from an open loop system without feedback control into a closed system controlled by a feedback mechanism. During this critical period, the actual environment modulates the development of the respective physiological control systems for the entire life period, especially through changes in neuronal-organization and expression of related effector genes.[17,18] One example could be Timothy syndrome,[19] where there is multiorgan dysfunction including lethal arrythmias, webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism from the Ca(V)1.2 missense mutation G406R, resulting in calcium overload. While this could be obvious at birth—as are other birth-related defects (i.e., cerebral palsy and spina bifida)—most neuropsychiatric disorders on the other hand are not apparent until later.

Early childhood/adolescence. Disorders like autistic spectrum disorders, Asperger's syndrome, ADHD, mental retardation, major depressive disorder (MDD), and generalized anxiety disorders (GAD), unlike Huntington's chorea (HC) and other well established heritable disorders, are more elusive, but manifest earlier in the developmental process. There is an abundance of literature[20–22] associating these conditions with calcium dysregulation, calcium signaling, and altered calcium homeostasis. Therefore, neonatal and postnatal calcium homeostasis versus *in-utero* calcium homeostasis in the brain clearly become intriguing as we explore these conditions. *In-utero* calcium homeostasis hypothetically should correspond to maternal calcium homeostasis. However, at this time it is unclear if maternal calcium levels have any impact on fetal brain calcium homeostasis either prenatally or postnatally.[23–25]

Early adulthood. Schizophrenia and bipolar disorder clearly present as early adulthood manifestations and are more site specific, i.e., associated with the dorsolateral prefrontal cortex as per recent literature.[26] The role of increased calcium binding protein, neuronal calcium sensor-1(NCS-1), in DLPFC of the brains of humans with schizophrenia and bipolar disorder has consistently been demonstrated by several groups.[27,28] Increased neuronal calcium sensor-1 (NCS-1), protein in a specific location (i.e., DLPFC) hypothetically raises the question of increased NCS-1 permeability through the BBB at this location in schizophrenia and bipolar disorder. Does that mean the BBB at this location is/was compromised? If yes, why during early adolescence and not sooner? Could this be biological, infectious, or environmental? While the answers for these questions remain open for discussion, evidence pointing to the central role of altered calcium homeostasis is becoming stronger. Furthermore, this theory was experimentally supported by another group[29] who by indirect methods (i.e., using therapeutic levels of lithium) inhibited InsP3 receptor enhancement of NCS-1 activity in schizophrenic and bipolar patients.

Recent efforts to establish calcium's central role in psychiatric conditions, such as schizophrenia and bipolar disorder, were supported by using the Boolean network model. Basically, the Boolean network model is a simple computational method used to explore the overall behavior of genetic networks and is represented by variables with two possible states (on/off) of the individual nodes/genes in the network. The authors[30] conclude that in addition to the expected components, dopamine and the dopamine receptor 2, Ca2+ ions play a critical role in maintaining the stability of the glutamate excitotoxicity pathway.

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Aging and metabolic conditions. Vascular-related depression and vascular dementia are well established age-related phenomena involving microcalcifications in several areas of the aging brain.[31] While these are irreversible, age-related chronic changes, other neurometabolic conditions, such as neuroleptic malignant syndrome and malignant hyperthermia, are associated with acute, reversible changes directly linked to cytotoxicity and altered calcium homeostasis.[32] Therefore, an argument can be made that some of the conditions discussed

here while as acute as they seem to be, could be amenable to early interventions and treatment, thereby preventing the progression to degeneration. Indirect calcium stabilizing effects in the brain using lithium have been found to be cytoprotective and neurotrophic.[33,34]

SUMMARY

Mobilization of calcium both extra- and intracellularly has tremendous implications in the brain because of its buffering capacity, especially in early brain development where the changes, if not corrected, could transform into irreversible pathology based on faulty/lower c-fos expression. Women, in general, have much less whole body calcium as compared to men and have a greater risk of deficiency as they age. The consensus for optimal calcium supplementation during pregnancy remains uncertain as there is currently insufficient available evidence.

However, we propose increased vigilance in blood calcium levels during pregnancy in addition to supplementing the recommended daily allowance to 1000mgs/day or slightly higher. Secondly, minimal doses of slow calcium channel blockers capable of passing through the BBB alone or in addition to conventional psychotropics would possibly prevent the progression and worsening of many conditions.

As practicing psychiatrists, we should be mindful of the cytotoxic effects of psychotropics and other medications that readily cross the BBB and which may have a lasting impact on calcium homeostasis at a very basic, molecular level, thereby increasing vulnerability to environmental and metabolic variations.

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